Docket No.: 20342/1202529-US1
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Richard Franklin

Application No.: 10/762,566 Confirmation No.: 3220

Filed: January 23, 2004 Art Unit: 1614

For: FORMULATION AND METHODS FOR THE TREATMENT OF THROMBOCYTHEMIA Examiner: A. R. Hughes

DECLARATION OF RICHARD FRANKLIN, PH.D.
UNDER 37 C.F.R. § 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

I, Richard Franklin, hereby declare and state as follows:

1. I am a citizen of Great Britain and over 21 years of age.

2. I received a B.Sc. in Biochemistry from the University of Wales, U.K. in 1967, a M.Sc. in the field of drug metabolism and pharmacokinetics from the University of Wales in 1970, and a Ph.D. in drug metabolism and pharmacokinetics from the University of Surrey, U.K. in 1975.

3. For almost 40 years, I have been designing experiments, managing, and consulting in the area of pharmaceutical drug metabolism and pharmacokinetics. I am currently the Senior Director of Exploratory Drug Development Projects of Shire Pharmaceuticals Development Ltd in Basingstoke, U.K. As Senior Director, I design and supervise experiments to test the feasibility of potential new drug products. I am the sole inventor of the invention described in the above-

captioned application and have assigned the invention to Shire Holdings AG. My curriculum vitae is attached as Exhibit 1 to this declaration.

4. I have read and am familiar with the text and pending claims, as amended in the Amendment submitted herewith, of the above-captioned application. The pending claims of this application set forth a method to treat thrombocythemia in a patient with thrombocythemia by transdermally administering a skin-permeable form of anagrelide or an anagrelide salt to minimize first pass liver metabolism.

5. I understand that the above-captioned application was filed in the United States Patent and Trademark Office on January 23, 2004. I also understand that the relevant date for evaluating obviousness of the application's pending claims is, at the very latest, this filing date.

6. In my opinion, the present claims would not have been obvious to one of ordinary skill in the art as of that date because such as individual would not have expected that transdermally administering a skin-permeable form of anagrelide to minimize first pass liver metabolism would circumvent the adverse cardiovascular side-effects observed when anagrelide is administered orally. This surprising result is discussed from page 2, line 14 to page 3, line 6 and from page 4, line 30 to page 5, line 4 of the application.

7. Between 24% and 40% of thrombocythemia patients orally treated with anagrelide fail to tolerate the drug due to marked heart palpitations and tachycardia. These undesirable symptoms were unexpectedly found to be caused by a metabolite formed during the extensive first pass liver metabolism of anagrelide. This surprising discovery was a result of studies that I supervised showing that (1) both healthy individuals and patients suffering from myeloproliferative disease who were orally administered anagrelide were exposed to more of the anagrelide metabolite, 3-hydroxy anagrelide, than anagrelide as measured by area under the curve (AUC) (*see* Example 10 starting on page 33, line 10 of the application), (2) the 3-hydroxy metabolite surprisingly showed an approximately forty-fold greater inhibitory activity towards phosphodiesterase III (PDEIII) compared to the parent anagrelide (*see* Example 9 starting on page 33, line 1 of the application), and (3) the cardiovascular effects of the metabolite included a dose-dependent increase in heart rate and

decrease in blood pressure (*see* Example 11 starting on page 34, line 9 of the application). Based on these studies and knowledge in the art that PDEIII helps to regulate the cardiovascular system, it was surprisingly concluded that patients, who were orally administered anagrelide, elicited profound inotropy and chronotropy because anagrelide was metabolized and its metabolite profoundly inhibited PDEIII causing these adverse effects.

8. This was a surprising discovery because the metabolite showed a remarkably high PDEIII inhibitory effect for such a relatively minor change to the structure of the anagrelide molecule and a metabolite causing undesirable side-effects represented the opposite of the expected metabolic detoxification process occurring in the liver. In light of this surprising discovery, I supervised the development of methods of treating thrombocythemia by transdermally administering anagrelide to minimize first pass liver metabolism and reduce the formation of the unwanted anagrelide metabolite. As part of this development, I supervised the study as described in Example 8 starting on page 30, line 20 demonstrating that less metabolite is produced in the plasma, but the same amount of anagrelide is available when anagrelide is transdermally administered compared to orally administered anagrelide as measured by AUC in mini-pigs, a species having skin with similar permeability compared to man.

9. A subsequent study was also performed to demonstrate the difference in the ratio of anagrelide and its 3-hydroxy metabolite in blood plasma when anagrelide was administered orally, using a dermal patch, or using an occluded, adhesive, stoma ring. Administration by either dermal patch and by dermal stoma ring are both methods of transdermal delivery . No systemic adverse clinical signs were observed during this study for any administration mode, however adverse skin reactions were observed in some animals during anagrelide administration using dermal stoma rings. Similar to the findings in the previous study described in Example 8 of the application, the ratio of anagrelide to 3-hydroxy anagrelide based on AUC_{0-t} was statistically significantly higher in dermal stoma rings (13.3±2.8) compared to the ratio after oral dosing (3.9±1.4). The ratio based on C_{max} values also showed that more anagrelide than metabolite was present after using a dermal stoma ring (6.1±1.9) compared to oral administration (3.5±1.2) (however the results with C_{max} were not statistically significant).

10. Measurable concentrations of anagrelide in the blood were not found after administration of anagrelide by dermal patch in the same subsequent study. Blood samples for blood platelets were taken prior to and after treatment by dermal patch, but there was not a clear tendency showing either an increase or decrease in the numbers. It is believed that the lack of anagrelide in the blood of minipigs administered anagrelide using a dermal patch in this study was a result of the lack of viscosity of the drug delivery vehicle and leakage through the retaining microporous patch membrane compromising adhesion to the skin. Further studies are being considered to overcome these mechanical difficulties.

11. In sum, in my opinion, one of ordinary skill in the art would have found it surprising as of the filing date of the present application that administering anagrelide to thrombocythemia patients by transdermal means to minimize first pass liver metabolism would reduce the undesirable side-effects observed when anagrelide is administered orally. This unexpected result was derived from the discovery that the 3-hydroxy metabolite of anagrelide is a potent inducer of adverse cardiovascular side-effects as compared to anagrelide.

12. I further declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further that these statements are made with knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under §1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the instant application or any patent issued thereupon.

Respectfully submitted,

Dated: 17 September 2007

Richard Franklin, Ph.D.

Exhibit: 1. Curriculum Vitae of Dr. Richard Franklin

Shire

CURRICULUM VITAE

Dr Richard Franklin

EDUCATION & QUALIFICATIONS

1975	**PhD (in drug metabolism and pharmacokinetics)** University of Surrey
1970	**MSc (by research in drug metabolism and pharmacokinetics)** University of Wales
1967	**BSc (Hons) Biochemistry** University of Wales

CAREER & EXPERIENCE

Jan 2006-present	**SHIRE PHARMACEUTICALS DEVELOPMENT Ltd, Basingstoke, Hants** ***Senior Director, Exploratory Drug Development Projects*** - Application of creative skills to the design and feasibility testing of potential new drug products. Outsourcing of all associated experimental activities covering synthetic chemistry, in vitro and in vivo pharmacology, toxicology, & DMPK.
Jul 200 to 2005	***Preclinical Sciences Manager*** - Outsourcing, management and reporting of all necessary preclinical, clinical pharmacokinetic/drug metabolism studies required for regulatory filings on assigned drug development covering pharmacology, toxicology, preclinical and clinical drug metabolism & pharmacokinetics.
Sept 99 to Jun 2000	**OSI PHARMACEUTICALS, Aston Science Park, Aston, Birmingham** ***Pharmaceutical Project Manager*** Role was to co-ordinate and progress drug development programmes for OS it's JV company with Pfizer, Anaderm
Feb 1999-Jul 1999 (Fixed term contract)	**ZENECA CTL, Alderley Park, Macclesfield, Cheshire** ***Pharmaceutical Projects Manager*** Role was to help design and manage multi-stranded pharmaceutical develop projects on behalf of Zeneca Pharmaceuticals as well as third parties placing at their Central Toxicology Laboratory.

1996 - Dec '98 **HUNTINGDON LIFE SCIENCES, Huntingdon, Cambridgeshire,**
European Business Development Manager, Chemistry Services
Role was to develop business in drug metabolism/pharmacokinetics, contract clinical pathology and formulation stability testing, visiting clients and present range of services, assisting them in the design and development of study pro for regulatory filings, and co-ordinating enquiry responses.

Feb '95 - Feb '96 **PHARMACO -LSR, Eye, Suffolk**
Associate Director, Pharmaceutical Projects Co-ordination Directorate
Role was to advise prospective clients on appropriate drug development strat - especially re. drug metabolism & pharmacokinetic studies - and to co-ordina such studies as part of a multistranded programme on their behalf.
To direct ongoing projects within Drug Metabolism and Pharmacokinetics & t promote the DMPK services.

Jan'93 - Jan '95 ***Operational Manager, Drug Metabolism, Bioanalysis and Pharmacokine***
Manage dept of 25 staff conducting work on drug metabolism and pharmacokinetics for third party clients.

June '91- Dec '92 **STERLING WINTHROP PHARMACEUTICALS RESEARCH DIVISION, Northumberland,**
International Associate Director, Drug Metabolism
Responsible for the management and direction of all metabolism studies, Managed some 28 staff, 14 in the UK and 14 in the US.

Manager and Head of UK Dept of Metabolism, Pharmacokinetics and Cl Pharmacology Management and direction of all metabolism, pharmacokinet clinical pharmacology studies conducted in the UK. Staff of 25

1972 - '86 **WYETH LABORATORIES (UK) LTD, Maidenhead,**
Head of Drug Metabolism and Pharmacokinetics
Management and direction of all metabolism & pharmacokinetics studies conducted in the UK. Staff of 10.

1968 -'72 **BDH (RESEARCH) DIVISION OF GLAXO, Godalming**
Section leader, Dept of Biochemistry
Conduct and management of metabolism & pharmacokinetics studies Staff of 3

Name – Dr Richard Franklin

PUBLICATIONS.
Forty-five publications in preclinical and clinical drug metabolism and pharmacokinetics.

PRESENTATIONS
Numerous presentations on all aspects of preclinical and clinical drug metabolism and pharmacokinetics at Drug Metabolism Discussion Group meetings as well as other national and international meetings.

MEMBERSHIPS
Past member of Drug Information Agency
Past member of Academy of Pharmaceutical Sciences
Past member of British Pharmacological Society
Past member of International Society for Study of Xenobiotics

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Signature Date